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Topic

"QbD BASED ANALYTICAL DEVELOPMENT AND VALIDATION OF HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY METHOD FOR QUANTIFICATION OF DRUG AND IMPURITIES FROM PHARMACEUTICAL DOSAGE FORM"

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1. ABSTRACT:

Now days, Quality by design (QbD) is considered an important, fundamental, and integral part of drug form development. Despite its significance in drug formulations, the knowledge, reference, and guidance for using QbD in analytical science have not been thoroughly documented in the literature. The traditional analytical method development based on variation of on one factor at a time (OFAT) to evaluate method change and identification of risk into method. This also causing narrow robust method which further has high risk in method failure and always requires revalidation protocol after method transfer or alternative method development; thereby it has been increasing the cost of the method. However, to overcome this potential factor from life cycle of drug; industry and regulatory introduced scientifically based analytical QbD to developed the analytical method and validated as per ICH Q2 guidance.

The present study is aimed to study application of QbD into development of robust HPLC methods by using it different tools like design of experiments (DOE) by studying multiple variable factors at a time, which benefits to get best method operated region. This involves identification of critical quality attributes (CQA) and method operable design space (MODS). This study further explores in assessment of risk into method and its lights on controlling it. This overall principle exclusively applied in development of high-performance liquid chromatography (HPLC) method for quantification of drug and impurities from different dosage form. The developed method further validated as per ICH guidelines.

2. INTRODUCTION:

In this era of competition quality has been given prime magnitude; failure to meet such quality allied goals produces massive shift of company in share of market. In this context pharmaceutical industry is utmost regulated industry as it is governed by authoritative regulatory bodies. Quality is very important in drug for patient safety and trustworthiness for accurate treatments. The regulatory bodies for pharmaceutical products give more importance to the quality of drug product. These bodies have provided different guidance and imposing industry to implements quality by design concept into drug developments to avoid further hurdle of failure in drug results and loose quality overtime. The pharmaceutical industries are investing billions of moneys in the drug discovery and development process with endeavor to design quality product and that to with consistency in manufacturing process to deliver the intended performance of

product. The industry focused on customer satisfaction and customer demands the perfection in quality, reliability, low cost and timely performance. Customer satisfaction can be achieved by two ways i.e. features and free from deficiencies in goods. The features like performance, trustworthiness, robustness, ease of use, and serviceability have to build in the product and such product should be free from deficiencies. Quality, productivity, cost, cycle time and value are interrelated terms. Quality activities must try to detect quality problems early enough to permit actions without requiring compromise in cost, schedule or quality. The emphasis must be on precaution rather than on just correction of quality problems. Quality can be the driving force to empower results in other parameters. Hence the quality has to be built in the product as well as services through proper planning, so that the forth coming failure can be avoided. Mere analysis of final product will not work but the quality should be designed in the product.

The concept of quality by design was summarized by a well-known quality expert Joseph Moses Juran; he believed that quality could be planned and that most quality associated problems have their origin in the way which quality was planned in the first place. The principles of QbD have been used to advance the product and process quality in every industry and in pharmaceutical industry regulatory bodies taken serious note on it and acknowledged that more and more controls were required for drug manufacturing processes for efficient drug product and no doubt for better regulatory decision making. It resulted in more stringent regulatory upbringing.

QbD involves thorough understanding of process; a goal or objective is defined before actual start of process. Design space and real time release risk assessment are other parameters for implementation of QbD. International conference on harmonization in its Q8 pharmaceutical development, Q9 quality risk assessment and Q10 pharmaceutical quality system gives stringent requirements regarding quality of product. FDA also states the importance of quality of pharmaceutical products by giving Process Analytical Technology (PAT) which is a framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance. Now industry started implementing QbD in drug formulation development process and in analytical method development. [1-8]

QbD does not necessarily mean less analytical testing'' rather, it means the right analysis at the right time, and is based on science and risk assessment. Implementation of QbD helps to develop rugged and robust method which helps to comply with ICH guideline and desired specification in

drug required at different stages of drug development. Factors which improve robustness are taken into consideration for the development of analytical method in QbD environment. It suggests that approaches like target profile, CQA, design space, and risk assessment are applicable to analytical method also. Though it is not adopted by all pharmaceutical industries it has future perspective because it may become mandatory by regulatory bodies. Voluntary adoption of this concept by industries is possible because of its various benefits, and ease of compliance with regulatory authorities. Pharmaceutical research and manufactures of America (PhRMA), Analytical Technical group (ATG) and European Federation of Pharmaceutical Industries and Association (EFPIA) have given clear ideas about parallel implementation of QbD to analytical method.

Potential benefits of adopting QbD for analytical method

- The developed method will be more robust which gives greater level of confidence in case of variations in conditions.
- This approach gives greater transfer success when method is transferred from research level to quality control department.
- It provides a space for invention of new techniques by continuous improvement throughout life cycle.
- It helps for enhanced understanding of the method.
- Design space concept avoids the post-approval changes which may cause to pay a high cost for any of the firm. It provides greater compliance with regulatory authorities.

Amongst all chromatographic techniques the High-performance liquid chromatography (HPLC) is mostly used technique in drug analysis due to it imitable characteristic of sensitivity, reproducibility and diversity in detection of molecular properties. Hence it is vital to apply QbD principle to develop stability indicating method HPLC methods with different detectors. These applications generate robust method and also find control strategy by assessing various mathematical models in QbD. [9-18].

3. BACKGROUND

In present days, analytical method failure is becoming more common especially during method transfer as well as in quality control departments. It is presumed to be due to the exception given for robust test compliance by ICH Q2 guidelines. In current practices, chromatographic methods are more commonly employed as right analytics at all the stages during the product life cycle. Common analytical methods for content uniformity, assay, impurity profile, and stability indicating assay are based on high performance liquid chromatographic (HPLC) or ultra performance liquid chromatographic (UPLC) or rapid resolution liquid chromatographic methods (RRLC). In connection with chromatography, due to complex parameters involved in the method development phase, low sensitivity, selectivity, and inadequate understanding between method performance and method parameters, always the revalidation protocol has been recommended in procedures. On the other hand, in current practice, the implemented analytical methods were based on one factor at a time (OFAT), in which one parameter alone is optimized for the expected response whilst others remained constant. This practice always yielded a narrow robust behavior of the method for instrumental variables used in method development phase. Hence the present strategy of analytical method (i.e.,OFAT) development has high risk in method failure and always requires revalidation protocol after method transfer or alternative method development; thereby it has been increasing the cost of the method.

The Analytical quality by design (AQbD) explores scientific understanding in method implementation sequences and starts with product quality that relates the risk assessment in method choice and then between method parameter and expected method results. These produce a region for high robust and cost-effective approach. DoE is an also part of AQbD, and it represents the interaction among the input variables that ultimately affect the method response and results. At this juncture, AQbD paradigm is a preferred and recommended strategy to be followed in analytical method development so as to attain regulatory flexibility and reduce out- of-trend (OOT) results, out-of-specification (OOS) results, out-of-control (OOC) and out-of-statistical-control (OOSC) by concluding. The present scope of this research to develop robust analytical method for quantification of drug and impurities from pharmaceutical dosage form. Subsequently, the developed method is validated as per requirement of ICH Q2 guidance.

4. LITERATURE REVIEW:

[Lawrence X. Yu, et al., (2008)] had studied pharmaceutical Qulity by design (QbD) in quality control of pharmaceutical drugs which has been defined predetermined approach which is critical quality attributes in product developments. He had evaluated different QbD elements in designing and formulating product developments with simultaneously stdying CQA in analytical methods to be control during developments. Finally concluded that the pharmaceutical QbD; how it can be used to ensure pharmaceutical quality throughout in product cycle.

[Lee SL, Raw AS, Yu L; (2008)] had examined the QbD principles in analytical method development with holistic approach and explained about how it advantages over old methodology of analytical development. It also reviews about regulatory requirement about QbD. It has explained in details about method development strategy (MDS) approach for QbD analytical. These also explain about method scouting and evaluation, method goals inQbD. Process of QbD in details with examples of imputiyy profiling. It also included validation of these methods with applied QbD concepts. These peoples utilized Mini tab software for whole study.

[Karmarkar et al; (2011)] had provided details application of Quality by Design (QbD) concepts to the development of a stability indicating HPLC method for a complex pain management drug product containing drug substance, two preservatives, and their degradants is described. The QbD approach consisted of (i) developing a full understanding of the intended purpose, (ii) developing predictive solutions, (iii) designing a meaningful system suitability solution that helps to identify failure modes, and (iv) following design of experiments (DOE) approach. The starting method lacked any resolution among drug degradant and preservative oxidative degradant peaks, and peaks for preservative and another drug degradant. The method optimization was accomplished using Fusion AE™ software (SMatrix Corporation, Eureka, CA) that follows a DOE approach.

[George L. Reid, et al; (2013)] had consist of AQbD concept and explaining details about Analytical target profiles. They included AQbd workflow included each steps in analytical development. Each step has intercorrelation with each other and this relation explained with proper justifications. As per ICH Q2B and USP method performance characteristics divided into

different category based on risk associated with it. These also included development flow and its steps. They plotted DOE and proof variability in method parameters. They were identified methods parameters which are impacting as poor method robustness. They proof how the method meets its intended performance requirements throughout the product and method lifecycle.

[Richard Verseput et al; (2015)] had involved details procedure of development of dissolution methods for various drug using QbD concepts by utilizing S-matrix fusion software. These development studies had involves evaluation different Quality analytical target profiles by evaluations robust range in different parameter in dissolution conditions. Study concluded critical quality attributes (CQA) which strongly impacts on dissolution performance of dosage form. He concluded dissolution behaviors with change in CQA. These studies had involves robustness study with mentioning tolerance limits.

[Jaiprakash N.Sangshetti et al; (2017)] had described role of different regulatory bodies viz. USFDA, ICH and WHO. They also elaborated ICH Q8-Q11 chapter establishment procedure and it requirement. They also elaborated about Regulatory challenges and inspection in pharmaceutical quality audits and how QbD reduces burden in quality audits. They also described method, procedure, interpretation of QbD data. They included tool used in QbD. Risk assessment procedure and provided details about input variable and CQA. Risk assessment tool are Ishikawa or fishbone diagram, Failure mode effect analysis (FMEA), Pareto analysis. This article is included life cycle of product development and QbD approach to improve quality at each step.

[Aarna R. Dedania et al; (2021)] had included basic concepts of QbD and current regulatory requirement from pharmaceutical industry. They elaborated about issue highlighted over the years include poor cGMP compliance and lack of understanding regarding the product and process parameters. This issue how generated and it impacts on consumer skepticism. They concluded regarding the quality of pharmaceutical products, especially the generic medicines by improved through QbD concepts. They also touched how global regulatory agencies ICH and US FDA tackle poor cGMP compliance. They were endeavors to provide an overview account on various facets of QbD in pharmaceutical development for ultimately attaining manufacturing excellence and regulatory compliance.

5. RATIONAL OF STUDY

Each day regulatory authority has issued numerous critical quality observations to pharmaceutical companies, which heavily impacting pharmaceutical reputation and loss of billions money. Hence Pharmaceutical industry is constantly searching the ways to ensure and enhance product safety, quality and efficacy. However, drug recalls, manufacturing failure cost, scale up issues and regulatory burden in recent past produce huge challenge for industry. In traditional, the product quality and performance are predominantly ensured by end product testing, with limited understanding of the process and critical process parameters. Therefore; in product development control strategy tool are required to assess risk before and during product development, which assists forecast failure of drug product in life of drug. Hence today pharmaceutical world important tool QbD was introduced, which has science-based approach was introduced which helps in understanding process by reducing variation and the enabling process control strategy. Regulatory body is also focusing implementation of QbD to control quality of drug product and satisfy patient need. Our intent is to develop various novel HPLC analytical methods by applying QbD principle. The method is assessed to analyzed quantification of drug from different pharmaceutical dosage form. The development method will be validated as per ICH Q2 for its specificity, reproducibility, linearity, accuracy and robustness. The method development also optimized for quantification of impurities generated into drug product by using different detector techniques. The main rational of this research is to make available the robust analytical method for assessing accurate drug and impurities from drug products at it different life cycle.

6. AIM AND OBJECTIVE :

AIM:-

To develop and validate RP-HPLC analytical method by using different detectors by QbD approach, for quantification of active content and impurities from drug product.

OBJECTIVE:-

1. To develop analytical method for quantification of drug.
2. To evaluate different detectors for accurate quantification.
3. To apply QbD software for optimization and identification of method.
4. To study robustness of method by QbD software.
5. To study impurity profiling for degradation product.
6. To validate, optimized method as per ICH guidelines.

7. PLAN OF WORK

To achieve these objectives, following plan of work will be execute:

1. Literature survey on the research topics.
2. Procurement of required chemicals, drug products, drug substances, impurities, surfactants and chromatographic columns for dissolution and analytical method development.
3. Selection of drug products candidates for analytical and dissolution developments on the basis of rational for development.
4. To procure access of different QbD development software's.
5. Development of different analytical methods with QbD strategic approach and perform method Scouting, control strategies and evaluation. Method Selection and Risk Assessment.
6. Validation of analytical and dissolution method as per regulatory guidelines by using QbD software after post method development.
7. Evaluation of risk assessment in methods.
8. Quantification of active drug and impurities profiling and reporting.
9. Data compilation and interpretation.
10. Data reporting and submission.

8. DURATION OF THE PROJECT:

Sr no	WORK	PERIOD
01	Literature review	06 Months
02	Procurement of required ingredients and necessaries	06 Months
03	Development of different analytical methods with old methods	08 months
04	Application of QbD strategic approach and subsequently validated with MDS methods.	08 months
04	Compilation of risk assessments in each method and define design space.	03 months
05	Quantification of active drug and appropriate impurities.	02 months
05	Data evaluation and write up	03 months

9. RESEARCH OUTCOME

The outcomes of this research for developing methods via QbD principles include enhanced understanding of (method and instrument) risk factors that may lead to poor method robustness. To overcome the risk and make method more reproducible to ensure that the method meets its intended performance requirements throughout the (product/method) lifecycle.

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